CHEMISTRY OF TWISTANE SYSTEM AND ITS USE IN STEREOCHEMISTRY*

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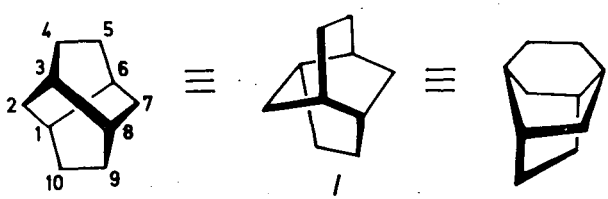
The aim of the present review is to show the chemistry of twistane system and the various ways in which it can be used as a stereochemical model of great utility. Many of the stereochemical applications mentioned are the result of investigations made in the author's Laboratory.

Twistane — tricyclo(4,4,0,$0^{3,8}$)decane (**I**) — belongs to the great family of adamantane isomers** of the formula $C_{10}H_{16}$. It is composed solely of six-membered rings, twisted in the same sense. The parent hydrocarbon has three two-fold rotational axes of symmetry (D_2) and exists in two enantiomeric forms which differ in the sense of twist: according to the CAHN—INGOLD—PRELOG nomenclature [11] the enantiomer (**Ia**) has *P*-helicity whereas the other (**Ib**) *M*-helicity.



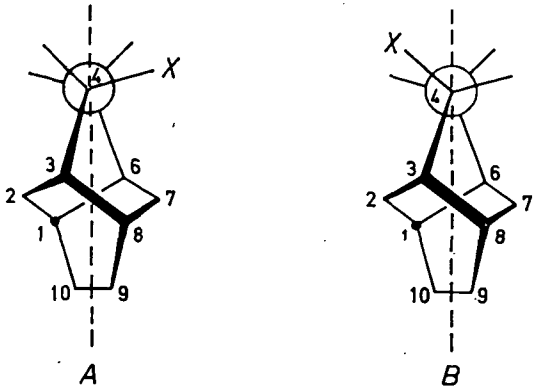
I

Ia *Ib*

* This review is based on a lecture presented at A. József University, Szeged, and on the review in Chem. Listy **69**, 45 (1975).

** For reviews on adamantane chemistry see [1—3], adamantane isomers other than twistane are studied e.g. in ref. [4—10].

There are three groups of sterically analogous carbon atoms in this system: carbons 1,3,6,8, carbons 4,5,9,10 and carbons 2 and 7. Whereas the two bonds at $C_{(2)}$ and $C_{(7)}$ in the parent hydrocarbon are sterically equivalent, the bonds in positions 4,5,9 and 10 are non-equivalent and therefore substitution in these positions affords two diastereoisomeric (monosubstituted) derivatives (Formulae **A** and **B**).

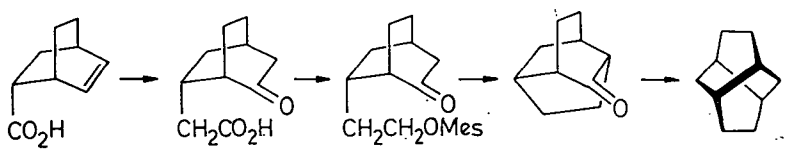


It has been suggested [12] to denote the isomers according to the position of the substituent relative to the carbon $C_{(1)}$: if the substituent is on the same side of the molecule as the carbon $C_{(1)}$ the configuration of the epimer is *endo*. Another alternative was suggested by MUSSO [13].

A generally applicable, though somewhat cumbersome, way of description is the use of the R—S nomenclature [11]. Thus, the isomer **A** (*exo*-4-X-twistane) would be called rel(1S, 3S, 4S, 6S, 8S)-4-X-tricyclo(4,4,0,$0^{3,8}$)decane (under assumption that the substituent X has higher priority than the carbon atom in the sense of the Sequence rule).

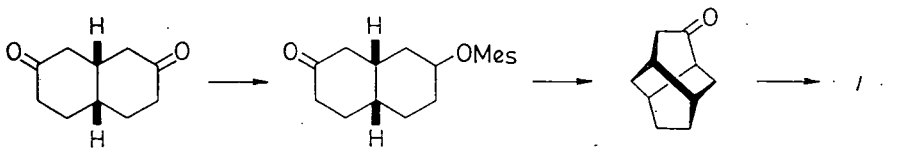
Preparation and Formation of Twistane System

Twistane was first synthesized by WHITLOCK and SIEFKEN [14, 15] in 1962 (Scheme 1). This synthesis started from *endo*-bicyclo(2,2,2)oct-5-ene-2-carboxylic acid (**II**) and its crucial step was the cyclization of the keto mesylate (**III**) to 2-twistanone (**IV**).



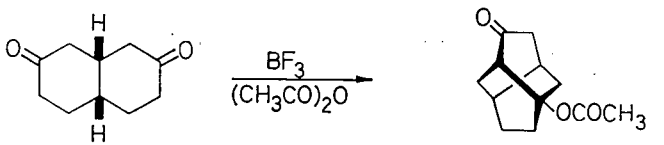
II *III* *IV* *I*

Another synthesis, carried out by DESLONGCHAMPS [16] and his co-workers, is substantially simpler and allows to prepare 4,5-vicinally disubstituted twistane derivatives *(vide infra)*. The starting compound is *cis*-decalin-2,7-dione (V) (Scheme 2).



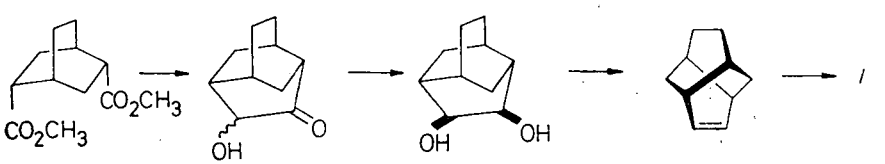
V VI

Later, this synthesis was shortened [17] practically to one step (Scheme 3).



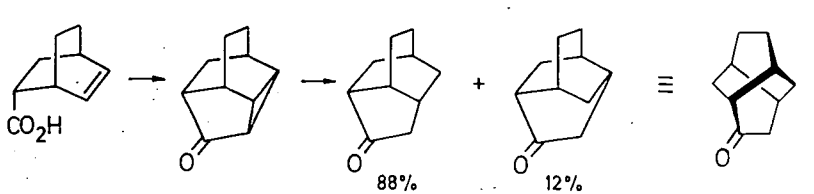
V

TICHÝ and SICHER [18, 19] devised also a simple synthetic approach which was used in the synthesis of twistene (**IX**) and which allows to synthesize also optically active derivatives. The reaction sequence is depicted in Scheme 4, the starting compound being dimethyl *endo*, *endo*-bicyclo(2,2,2)octane-2,5-dicarboxylate (**VII**) (Scheme 4).



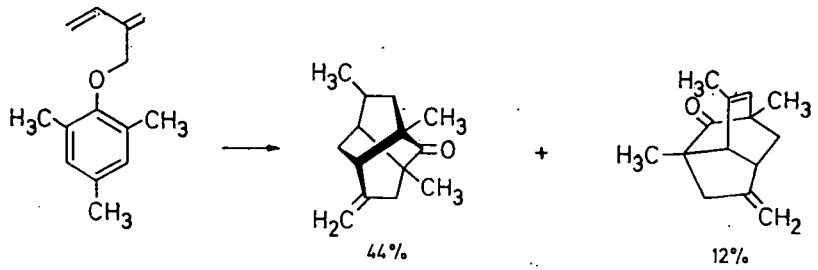
VII VIII IX

Also the possibility of hydrogenolysis of the tetracyclic ketone **X** over palladium was studied [18] (Scheme 5). This treatment, however, afforded only about 12% of 4-twistanone (**VI**), the principal product being the isomeric ketone (**XI**). This method was, neverthless, very useful in an optical correlation *(vide infra)*.

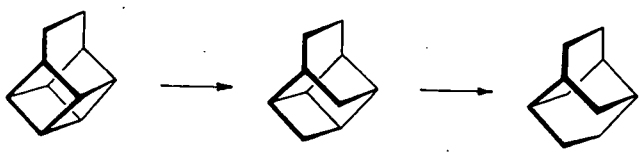


II X XI VI

Another reaction leading to substituted twistane derivatives was described by GREUTER and SCHMID [20] (Scheme 6.)

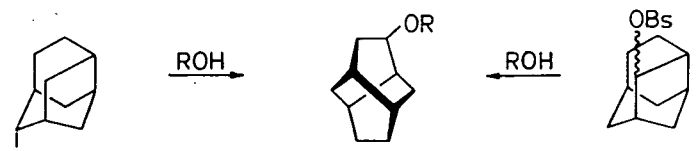


Hydrogenation of basketane (**XII**) and its derivatives [13, 21] affords also twistane or its derivatives as principal products (Scheme 7).



XII

Small quantities of twistyl products are formed in the solvolysis of 2- and 10-protoadamantyl tosylates [6, 22] (**XIII** and **XIV**, Scheme 8).

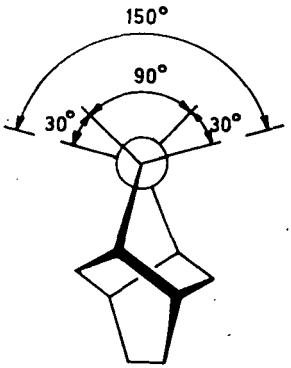


XIII *XIV*

Many synthetic pathways leading to twistane system were invented by artificial intelligence [24], including the actually used synthetic approaches.

Twistane as Stereochemical Model

Thanks to the twist of the whole molecule, the torsion angles between the bonds in positions 4 and 5 are about 30°, 90° and 150° (Formula C). All these are angles which are difficult to achieve in the common conformationally fixed systems. It is therefore possible to use the system as a model for studying the dependence of the reactivity (or interactions) of vicinal substituents on the torsion angle between the vicinal bonds. The knowledge of such dependence is of primary importance

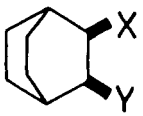
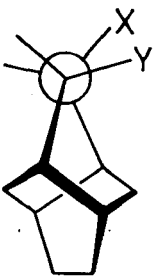
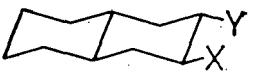
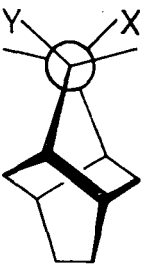
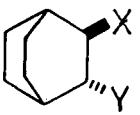
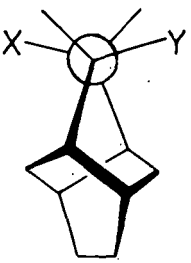
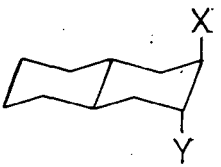


C

in the assessment of the reactivity or the energy of a given conformational situation. For such investigations it is necessary to have some rigid "standards" with defined torsion angles. The choice of the simple systems which served as yet as such standards was very meagre and the twistane system with its angles 30°, 90° and 150° fills very

Table I

Systems Used as Standards with Fixed Torsion Angles

System				
Torsion angle	0–10°	30°	60°	
System				
Torsion angle	90°	120°	150°	180°

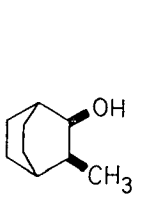
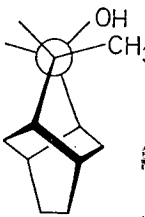
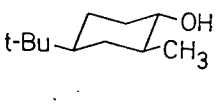
well the gaps in the present "scale" (Table I). Particularly the 90° angle is very interesting since for many reactions involving two vicinal substituents it represents an arrangement with the smallest overlap of orbitals.

For the study of the dependence of reactivity and vicinal interactions on the torsion angle, some 4,5-disubstituted twistane derivatives were prepared [12, 25].

Equilibration studies [12] of epimeric 4-hydroxy-5-methyltwistanes showed the magnitude of the repulsive interactions between OH and CH_3 groups in the isomers with 30° torsion angle. From Table II, where also values for other torsion angles are listed, the dependence on the torsion angle is clearly to be seen.

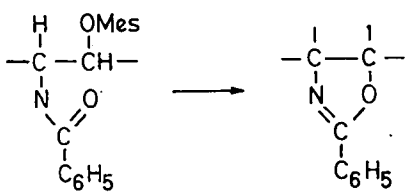
Table II

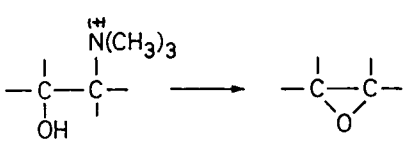
Vicinal OH/CH_3 *Interactions,* ΔG_{vic}, *in Various Systems with Fixed Torsion Angles*

Model			
Torsion angle	0–10°.	30°	60°
ΔG_{vic} (kcal/mol)	3.6	2.0	0.4

Concerning the attractive interactions, the hydrogen bond in vicinal amino-alcohols, dimethylamino alcohols and hydroxy esters was studied [25]. Here again the twistane derivatives filled the gaps in the present scale of models. Thus, it was found that the $\Delta\nu$ value for the torsion angle of about 30° is surprisingly similar to the value for the eclipsed conformation with an approximately zero torsion angle.

Of particular interest is the fact that the twistane aminoalcohol with the torsion angle 90° exhibits hydrogen bonding, even though the $\Delta\nu$ value is very small. The enthalpy of this hydrogen bond was estimated [25] to be about 1.5 kcal/mol. Also the corresponding hydroxy ester has a weak hydrogen bond.

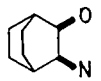
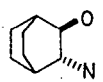
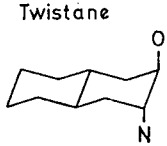




The relation between torsion angle and reactivity was studied [26] using two reactions: cyclisation of N-benzoyl O-methanesulphonyl derivatives of 2-amino-alcohols to Δ^2-oxazolines and epoxide formation from quaternary hydroxides derived from 2-amino alcohols (Scheme 9). It was found (Table III) that the twistane derivative with the torsion angle 90° still predominantly gives the five-membered oxazoline ring, whereas the geometrically more demanding cyclisation to the three-membered epoxide does not occur at all.

Table III

Cyclisation of Vicinal Benzamido Methanesulphonates and Quaternary Bases in Various Systems with Fixed Torsion Angles

Angle	System	Benzamido Mesylates		Quaternary Bases[a]	
		Cyclisation	Solvolysis	Epoxide	Ketone
0°		—	100%	—	100%
30°	Twistane	—	100%	—	100%
90°	Twistane	72%	28%	No non-basic products	
120°		100%	—	35%	65%
150°	Twistane	Skeletal rearrangement		92%	8%
180°		100%	—	100%	—

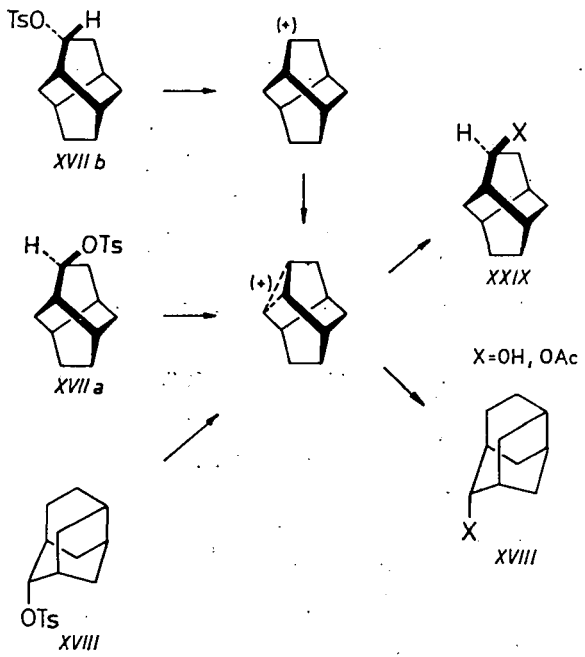
[a]Percentage based on non basic products.

Reactivity of the Twistane System

Strong Lewis acids, such as antimony pentachloride or aluminium tribromide, convert twistane into adamantane without any detectable intermediate [15]. Twistane is separated from adamantane (**XV**) by only one structure — protoadamantane (**XVI**) — and the isomerisation to adamantane goes energetically downhill [15, 27].

In contrast to the undiscriminative generation of carbonium ions by Lewis acids, leading to adamantane, the solvolysis of tosylates gives different products depending on the initial position of the tosyloxy group. Solvolysis of 1-twistyl tosylate gives solely 1-twistyl derivative, without any rearrangement [28]. On the contrary, 2-twistyl tosylate affords a mixture of about eight compounds, none of them being adamantyl acetate or 2-twistyl derivative [15].

We studied the solvolysis of the two epimeric 4-twistyl tosylates [22, 23] (**XVIIa** and **XVIIb**). The *exo*-epimer (**XVIIa**) reacts by about three orders of magnitude faster than the *endo*-epimer (**XVIIb**), this large difference being indicative of an anchimeric assistance in the former isomer. Both isomers give approximately the same mixture of compounds in which the predominating product is 10-protoadamantyl derivative (**XVIII**; X=OH, CH_3COO—), the 4-twistyl derivative representing only a minor component (20—40%, acording to the solvent) (Scheme 10).



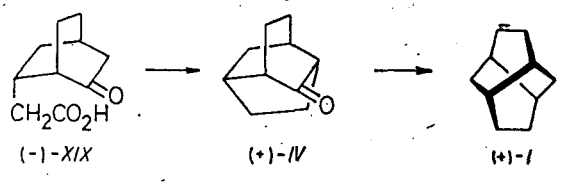
Adamantane derivatives were not found at all. The solvolysis of *exo*-10-protoadamantyl tosylate (**XVIII**; *X*=OTs) affords exactly the same mixture of products as *exo*-4-twistyl tosylate (**XVIIa**). The stereospecificity of the reaction is remarkable: both *exo*-4-twistyl and *exo*-10-protoadamantyl tosylate afforded only products of *exo*-configuration. Using detailed stereochemical study and deuterium labelling it was possible to explain the mechanism of these rearrangements [22, 23]. In all probability the common intermediate of the solvolysis of 4-twistyl as well as 10-protoadamantyl tosylates is a bridged carbonium ion which is then stereospecifically opened by the solvent (Scheme 10). Similar reaction course was observed also on heterotwistane derivatives, substituted in the analogous position [29, 30].

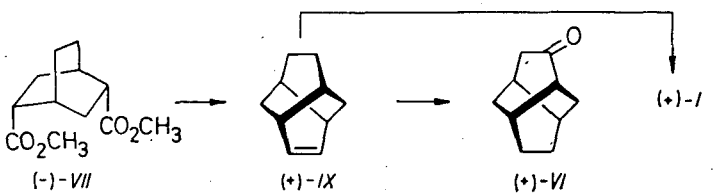
Since the reaction proceeds via a common intermediate, it was possible to calculate the energy difference between the twistane and protoadamantane system using the GOERING—SCHEWENE free-energy diagram [31]. The 10-protoadamantyl derivative (**XVIII**) was thus found to be by 4.4 kcal/mol more stable than the *exo*-4-twistyl derivative (**XVIIa**). According to calculations of SCHLEYER [32], protoadamantane should be by about 7.8 kcal/mol more stable than twistane.

Optically Active System

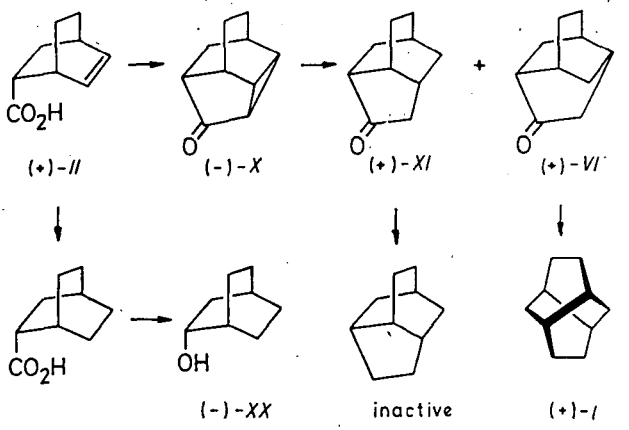
As already mentioned above, the twistane system is chiral and it can exist in two enantiomeric forms (**Ia** and **Ib**). The same holds also for heterotwistanes (see p. 166). Twistane is a very suitable (if not fundamental) model for the study of the so-called permolecular chirality, i.e. chirality which is due to the asymmetry of the molecule as a whole.

The first attempt to prepare optically active twistane derivatives and to determine their absolute configuration was made by ADACHI [33] and co-workers. These authors prepared optically active (+)-twistane ((+)-**I**) from the optically active keto acid (−)-**XIX** via 2-twistanone (+)-**IV** (Scheme 11). TICHÝ and SICHER [19, 34] prepared (+)-twistane and (+)-twistene according to Scheme 12.





Absolute configuration was assigned [33] to (+)-**IV** on the basis of ORD studies, using the KLYNE—DJERASSI rule [35]. The same absolute configuration was deduced later from the optical properties of (+)-4-twistanone [19]. Also the application of the SCOTT—WRIXON rule [36] to (+)-twistene led to identical result [34].



Because these assignments were made only on the basis of empirical optical methods, it was necessary to determine the absolute configuration by an unequivocal chemical correlation. The crucial compound was the optically active (+)-*endo*-bicyclo (2,2,2)oct-5-ene-2-carboxylic acid, (+)-**II**, (Scheme 13) which was correlated on the one hand with (−)-bicyclo(2,2,2)octan-2-ol ((−)-**XX**) of known absolute configuration [37—40] and on the other hand with (+)-twistane by two independent series of reactions [34].

Surprisingly, both these correlations revealed that the absolute configuration is opposite to that derived from the optical measurements. Further studies have shown that some of the rules, applied to optically active twistane derivatives, are valid, whereas other rules are not, (*cf.* [41]). The decisive factor in this system is in some cases evidently not the chromophore itself (ketone, double bond, etc.) but the permolecular chirality of the molecule.

This view is also supported by the fact that all the known optically active derivatives of twistane and heterotwistanes with the same helicity have the same sign of optical rotation (Table IV).

Table IV

Specific Rotation Values for Various Systems of Twistane Type

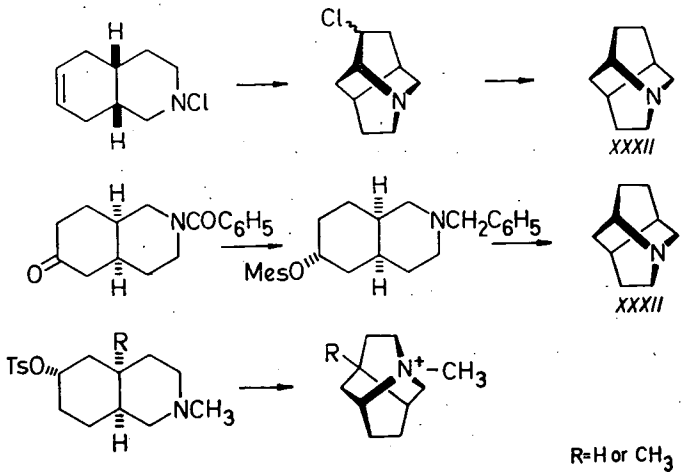
Compound	Formula		Ref.
(M)-Twistane	**Ib**	+434°(+355°)[a]	[34]
(M)-Twistene	(+)-**IX**	+417°	[34]
(M)-2,7-Dioxatwistane	(+)-**XXVIa**	+217°	[44]
(M)-4-Azatwistane	(+)-**XXIII**	+423°	[51]

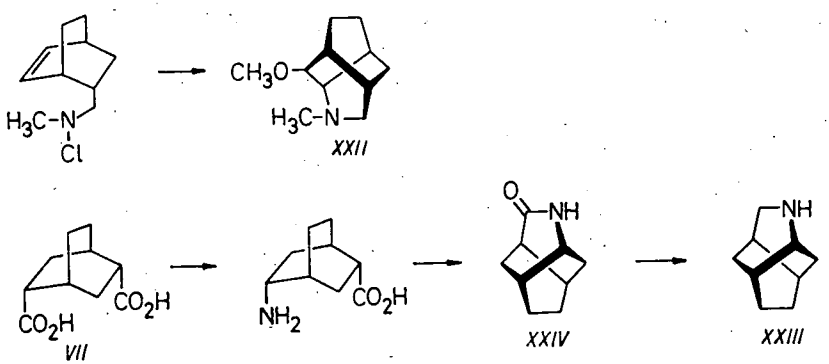
[a] Calculated by BREWSTER [24].

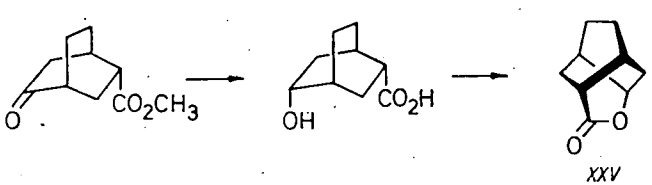
It is worth notice that the rotation of (M)-twistane calculated [42] by the BREWSTER Helical Conductor Model [43] gives $[\alpha]_D$+355° which is in a good agreement with the found value (Table V). On the contrary, calculations [33] using the Conformation Disymmetry Model [45] give a low value and even a wrong sign of rotation.

Heterotwistanes

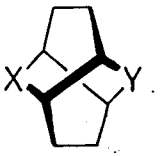
Systems containing one or two atoms of oxygen, nitrogen or sulphur were also studied. 1-Azatwistane (**XXI**) was prepared independently by several authors [46—49] (Scheme 14). A recent synthesis of a 4-azatwistane derivative (**XXII**) is reported [50]. Also 4-azatwistane (**XXIII**) itself was synthesized, both in the racemic and optically active form [51] (Scheme 15). Its derivative, 4-azatwistan-5-one (**XXIV**), was exploited as a valuable model of a twisted amide group with a defined angle of twist [52, 53] (Scheme 15). Also the oxygen analogue, 4-oxatwistan-5-one (**XXV**), prepared by LEE [54] (cf. [55, 56]), should be a promising model (Scheme 16).


H
NCl
H
Cl
N
N
XXXII
ref. [46]
H
NCOC6H5
O
H
MesO
H
NCH2C6H5
H
N
XXXII
ref. [47]
TsO
R
NCH3
H
R
N+-CH3
ref. [48,49]
R=H or CH3


H3C-N
Cl
CH3O
H3C-N
XXII
CO2H
CO2H
VII
NH2
CO2H
O
NH
XXIV
NH
XXIII


O
CO2CH3
OH
CO2H
O
O
XXV

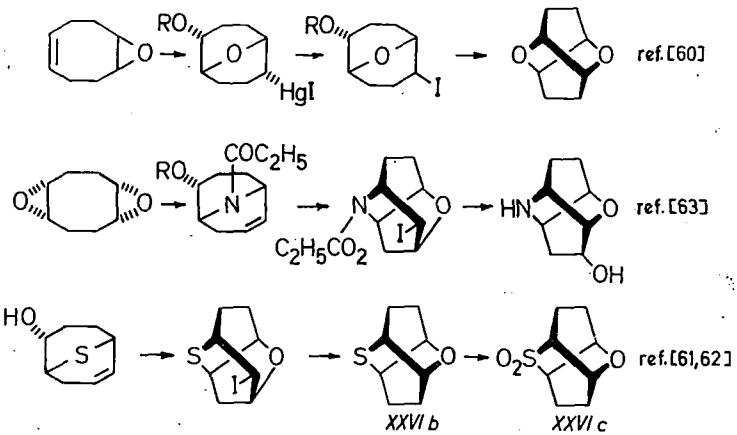
Systems with two hetero atoms in the twistane skeleton were investigated by GANTER and collaborators [57, 58]. A whole series of compounds of the type **XXVI**



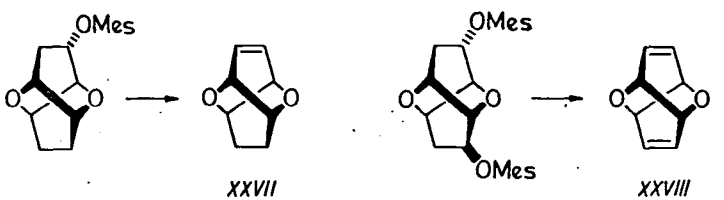
XXVI

a, X = O, Y = O ref. [30,44,58,59]
b, X = S, Y = O ref. [60]
c, X = SO_2, Y = O ref. [61]
d, X = NH, Y = O ref. [62]

was prepared [30, 44, 59—63]. Cyclooctadiene was used as starting material in all these syntheses (Scheme 17). Compound **XXVIa** was prepared also in the optically active form and its absolute configuration was determined [44].



The reactions of heterotwistane derivatives are similar to that of the carbocyclic system. Halides and tosylates with the reacting group in position 4 are solvolysed under partial or complete rearrangement to the corresponding heteroprotoadamantane derivatives [30, 57]. Unsaturated 2,7-dioxatwistene (**XXVII**) and doubly unsaturated 2,7-dioxatwistadiene (**XXVIII**) were also synthesized [64] (Scheme 18) whereas the carbocyclic analogue of **XXVIII** is still unknown.



Conclusion

As has been shown, the twistane system is a suitable model for the study of permolecular chirality and its relation to other forms of chirality. The twist of the molecule allows studies of steric situations caused by the uncommon torsion angles 30°, 90° and 150°. The six-membered rings of which the system is formed can serve as models of the usually elusive twist-boat form. Also, the rearrangements of the system are not without interest.

Recently, it was found that some twistane derivatives also exhibit antiviral activity [65, 66]. It is therefore evident that twistane system can be useful in more than one way and that the possibilities of its exploitation are far from being exhausted.

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ХИМИЯ ТВИСТАНОВ И ИХ ПРИМЕНЕНИЕ В СТЕРЕОХИМИИ

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В данном обзоре автор преследовал цель отражения химии твистанов и различные возможности их применения в качестве стереохимических моделей. Многие из упоминаемых в этой статье стереохимических применений являются результатом исследований проведенных в лаборатории автора.